Centers for Disease Control and Prevention
EARLY HEARING DETECTION AND INTERVENTION
Special Topics Teleconference
November 15, 2005

Presentation:

Congenital Cytomegalovirus (CMV) and Hearing Loss

TO: Special Topics Group for EHDI
FROM: Jamie M. Elliott
SUBJECT: Conference call information and agenda.
DATE: Tuesday, November 15, 2005

The next EHDI teleconference will be on Tuesday, **November 15, 2005** from **3:00 to 4:00 pm Eastern** time. To join in, call: **1-866-842-6975**. You will be greeted by an automated voice and asked to enter a CONFERENCE CODE. **PASSCODE: 218840 (plus the # key).** Please call in 5 - 10 minutes before the conference starts so we can begin promptly at 3:00. If you have any questions please contact Jamie Elliott (*jei2@cdc.gov* / 404-498-3018).

An internet based captioning service will be available at no charge during this teleconference. If you would like further information or to schedule use of this caption service, please inform Jamie Elliott *(jei2@cdc.gov* / 404-498-3018) or Michele Johnson (brl7@cdc.gov).

Powerpoint slides will be available online to facilitate the presentation and discussion. The slides will be available at http://www.infanthearing.org/checkpoint/cdc/. To view the slides, enter the user name *CDC* and the password *CDC*. Viewing the slides will work best if you have a high speed internet connection but is possible with a dial-up connection. (Note that the slides will be posted on the site closer to the call date.)

Agenda

1. **Welcome,** Jamie Elliott, CDC EHDI
2. **Overview of CMV,** Dr. Michael Cannon, CDC National Center for Infectious Diseases
3. **Congenital CMV and Hearing Loss,** Dr. Karen Fowler, University of Alabama, Birmingham
4. **Congenital CMV-related Initiatives at NIH,** Dr. Bracie Watson, National Institutes of Health
5. **Congenital CMV - Summary of Activities at CDC,** Dr. Danielle Ross, CDC EHDI
6. **Questions**

Speaker Biographies **(in order of presentation)**

Dr. Michael Cannon received his Ph.D. in epidemiology from Emory University where his

dissertation was on the epidemiology of human Herpesvirus 8. He currently works with the Herpesvirus Team, Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases. Dr. Cannon's primary research focus is the epidemiology and prevention of congenital CMV disease.

Dr. Karen Fowler is a Research Associate Professor in the Departments of Pediatrics, Epidemiology and Maternal & Child Health at the University of Alabama at Birmingham. Her research interests are the epidemiology of maternal and congenital CMV infection and outcomes following infection, especially sensorineural hearing loss. Dr. Fowler has served as PI on a study of congenital CMV infection and hearing loss in young children funded by NIDCD in the past, and participates in other research grants and activities in the Division of Infectious Diseases in the Department of Pediatrics. She is currently the Co-PI of the recently awarded contract to UAB from NIDCD on "The Natural History of CMV-Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn."

Dr. Bracie Watson is a Program Director in the Hearing Program of the National Institute on Deafness and Other Communication Disorders (NIDCD). He directs the extramural portfolio in genetics, immunology/immunogenetics, and infectious diseases (otitis media and CMV). He received his Ph.D. in Genetics and Human Genetics/Medical Genetics from Howard University after completing his dissertation research at the National Cancer Institute/Laboratory of Biochemistry. After postdoctoral training, he accepted a primary faculty appointment in the UAB School of Medicine, with secondary appointments in the Department of Microbiology and Genetics. Dr. Watson joined NIDCD in March 2003.

Dr. Danielle Ross is a Senior Service Fellow with the CDC EHDI program. Dr. Ross holds a Ph.D. in Brain and Cognitive Sciences from the University of Rochester, New York and a Masters degree in Speech and Language Pathology from McGill University in Montreal, Canada. Her activities at CDC include research studies on mild and unilateral hearing loss, participation in the Congenital CMV Working Group, writing collaborative papers on the prevention of congenital CMV.

Edited Transcript

(A CDC EHDI Special Topics Teleconference on *Congenital CMV and Hearing Loss* took place on October 25, 2005 and was re-presented on November 15, 2005. The presentation portion of this transcript is from the October 25, 2005 teleconference. The Question and Answer portion of the following transcript includes questions from both the October 25 and the November 15th teleconferences.)

Jamie Elliott: Why don't we get started? This is Jamie here at CDC, and I would like to say welcome to the teleconference today. And I would like to thank our speakers. At this time, I would ask you to please mute your phones when you're not speaking to eliminate background noise, and please do not put your phone on hold. In the past, music or messages have come on when people have used the hold feature. To avoid distractions, when you're not speaking, please just mute your phone or call back in if you need to answer another call or attend to other business.

This afternoon, we have a great call planned, and some forerunners in research will be presenting on the call. We're pleased to have Dr. Mike Cannon from CDC to provide an overview of congenital CMV and then Dr. Karen Fowler from the University of Alabama, Birmingham to speak specifically about congenital CMV and hearing loss; Dr. Bracie Watson from the National Institute of Health will speak on Congenital CMV initiatives at NIH. Finally, Dr. Daniel Ross will follow with a summary of the activities at CDC. Brief biographies for our presenters were sent with the agenda, so you should have received them in advance.

We're grateful to these speakers for sharing their time and expertise today. We generally post powerpoint presentation slides on the website, but there was a little bit of trouble with the site today, so I did email the presentations out to you. Two of the speakers will be using powerpoint presentations and referring to the slide numbers as they go through their presentations today. Today's teleconference is being transcribed, and it will be available in three weeks to a month. I'll send out an announcement to let you know when the transcript is available on the CDC EHDI website. So again, please mute your phone, and if you need to leave the call, please hang up and call back in. I'll turn it over to Dr. Michael Cannon to begin.

Michael Cannon: If you have the slides to follow along – on slide number one, you might find it strange that I'm talking about new vaccine development as a way of introducing CMV. But I think a lot of people are not aware of the very large public health impact of congenital CMV. So as you can see on slide one, the institute report looked at a bunch of different agents which might be priorities for vaccine development. And on slide two, CMV came out the most cost effective vaccine that's not currently available. While on to slide three-- before I go to the reasons why this is, you can look at the cost effectiveness, which is often measured in this way: cost per quality-adjusted life year saved. And you can compare a CMV vaccine to some other sorts of medical interventions, for instance nucleic acid testing for HIV, which costs $2 million per quality adjusted life year that you save, or mammography, which is usually considered a good buy, which costs $70,000 per quality saved. You see that CMV vaccine would actually save you $50,000 for each quality-adjusted life year that you save; so it's effective cost savings.

On slide number four, you can see why this is: Children born with congenital CMV can have a number of transient outcomes (I've highlighted some of them) such as vision loss and mental retardation, and often children will survive and live for a long time with these serious disabilities. For that reason, from an economic standpoint, if you can prevent congenital CMV, you can save a lot of money as well as reducing the public health burden.

On slide number five, you can get an idea from the Institutes of Medicine report what the actual disease burden is; approximately 400 deaths a year. Over 3,000 children with severe mental retardation, and 6,000 children with mild hearing loss and vision loss and mild retardation, and very high direct costs result from this.

And finally, as far as the impact of congenital CMV, you can see from slide six, that if you compare a number of important child illnesses and syndromes (and I should tell you here that the numbers are kind of rough, so this is a ballpark idea), CMV causes long-term sequelae, mental retardation, and the number of children who suffer from more well-appreciated or well-known

syndromes such as Downs or Fetal Alcohol Syndrome. So it's a large problem and the same can be said for deaths due to congenital CMV.

Moving on to slide seven-- the herpesvirus. What happens is the person can have an initial infection or the primary infection, and then the virus becomes latent and doesn't do anything. But later on it can reactivate, and you can have viral shedding or you can also become infected with a different strain of the virus. That's called re-infection. Reactivation and re-infection together are known as recurrent or secondary infection.

On slide eight: Where can you find CMV? If someone is shedding CMV can you find it in many different bodily secretions, but especially in saliva and urine, and it tends to be present in high numbers in saliva and urine. Shedding duration tends to be (and this is not for every adult, but it tends to be a relatively shorter term for adults) for young children, toddler age or younger, months to years. And this has important implications as far as transmission of the virus.

On slide number nine, how CMV is transmitted: It's basically through any close contact with bodily fluid secretion such as saliva or urine, but sexual activity is also a risk factor. Transmission can go from the mother to the child from breast-feeding and blood transfusion is a risk factor, as is organ transplantation. But there's no evidence that secretions are a mode for CMV.

Slide ten: This is important for diagnosing it from birth. And it needs to be done within the first three weeks after birth or you can't tell whether the child was infected pre-natally or post-natally. And this is important because if the child is infected post-natally, they're at no risk for disease unless born prematurely. So generally the risk comes from it and you can only identify congenital CMV if you have specimens from the first weeks after birth. The way to diagnose it is through diagnosis of the culture or methods of rapid detection. PCR is a valid way of diagnosis as well. The specimens used are urine and saliva. It's easy to collect, and as Karen might mention, people have looked at, and it appears to be feasible to use dried blood spots as a way of diagnosis and further work on that is going to be done.

Slide 11 has a lot of information on it, but I'll try to walk you through it. First of all, this is to give you an idea of what happens throughout the process of congenital CMV. So if you look at mothers, it varies by income and if they show up as green boxes on your slide, these are women who are immune. What that means is women who are positive prior to pregnancy. You can follow the arrows down from the boxes and see that a small percentage of children will have infection if the mother is sero positive prior to pregnancy; so it's not an absolute. So if you move to the middle of the slide and look at those susceptible-- the 45% of the women in higher income, and the 15% of women in the lower income, and the susceptible meaning sero negative, you can see that between one to four percent of the women will have an infection prior to pregnancy, and to the fetus occurs quite often, between 30 to 50% of the time. So prior to infection, is a much higher risk situation for the fetus. Then if you move on down and look at the blue boxes, you can see that as babies who are born with congenital CMV, many don't have symptoms at birth. 85 to 90% appear to be fine. And of those who are asymptomatic at birth, most are healthy, but five to 15% develop it. And moving to the left, 10 to 15% of those at birth, nine to 15% develop it permanently. So that's what happens with CMV during pregnancy.

Moving to slide 12, we start to think about what we can do to prevent congenital CMV or to deal with it. You can keep mom from becoming infected or infecting the fetus or you can minimize the sequelae. But there are other things that I'm going to talk about briefly. Not all of these things, but including vaccines, and educational interventions and something in a came out recently in the New England Journal of Medicine, immunization during pregnancy. So for time reasons I'm not going to talk about all of these things, but just give you a few of the highlights.

In slide 13, CMV vaccine, the group at UAB has shown that protection, being sero positive prior to pregnancy is a good thing, suggesting that a vaccine would be protective. The downside is that the vaccine development has been underway for over 30 years, and a lot of progress is being made, but nothing is immediately around the corner. So there are some vaccines being tested and it's possible within five or 10 years there may be something, but it's not on the immediate horizon.

Slide 14 - passive immunization during pregnancy; it was a study done where they received the immune globulin. The study found that those who received the hyper immune globulin had a lower risk of infection and a lower risk of disease; however, it's not clear that this paper is going to lead to a consensus as to whether this sort of treatment should be done in pregnant women who are suspected of having a child with congenital CMV. It was done as a trial, and among other things, one of the biggest questions was, there were fetuses who had clearly documented physical damage that seemed to be reversed by the anti-body treatment and that raised questions. So this study is very provocative, but it's not clear that there's enough evidence at this time for passive immunization to be a widespread strategy, so that remains to be seen.

Slide number 15 is something that suggests what can be done about congenital CMV immediately. And that is prevention through hygienic processes, in particular, hand hygiene. Studies have identified that pregnant women are at risk, and an important source of infection for pregnant women is young children, the ones who are shedding a lot of virus, and the transmission is close contact with bodily secretion. So it's believed that it can prevent transmission with pregnant women. And if you want more information on the case for improved hygienic practices, I've listed an article by Cannon and Davis that walks through the rationale for that. But basically the hygienic practices include thoroughly washing hands with soap and water after exposure to urine and saliva or after high-risk activities, as well as avoiding an exchange of saliva and that sort of thing.

Finally, slide 17 - The take home message is that congenital CMV is more common than we tend to appreciate, and it's a very big problem that needs to be dealt with. Because we know about transmission, we feel that women deserve to be informed about prevention and things that they can do to try to reduce their risk and number three is sort of a plug for while we're waiting for a vaccine. There are things that we can do, and we ought to start there. Thanks.

Jamie Elliott: Thank you, Dr. Cannon, Dr. Fowler?

Karen Fowler: Yes.

Jamie Elliott: Please go ahead. If you have questions for Dr. Cannon, please wait until the end of the call.

Karen Fowler: I would like to thank the CDC EHDI staff for inviting me speak to you this afternoon, and today I would like to give you a brief overview on the scientific literature on CMV-related hearing loss. Although I have quite a few slides I promise to be brief. As you can see in slide two, children with congenital CMV infection may have a variety of developmental and sensory sequelae, but the most common sequelae that occurs following infection is sensorineural hearing loss. Deafness or hearing loss associated with symptomatic CMV infection was first reported in 1964, with other studies to follow in the 1960s further describing hearing loss following symptomatic infection.

Slide four – in the 1970s other studies both at UAB and elsewhere demonstrated that hearing loss also occurred after inapparent or asymptomatic congenital CMV infection. Further studies in the 1970s and 1980s continued to characterize and describe the hearing loss that occurred in children with congenital CMV infection.

On slide six, I have listed some of the cohort or population based longitudinal studies started in the 1970s and 1980s. These were cohorts of infants who were identified with congenital CMV infection at birth and were then followed longitudinally. You can see that sensorineural hearing loss occurred in both symptomatic and asymptomatic infants and progressive and fluctuating losses were observed in some of the groups also.

Slide seven lists cohorts that were followed in the 1980s and 90s where similar characteristics of hearing loss were observed as were in the previous studies, and also all of these later studies documented delayed hearing loss in their cohorts. Summarizing from these studies, we can assume that 22-65% of symptomatic infants will have hearing loss whereas six to 23% of asymptomatic infants will also have hearing loss following congenital infection. Sensorineural hearing loss following congenital CMV infection may be present at birth or delayed presenting in the first years of life. The severity of hearing loss following congenital CMV infection may be variable, ranging from unilateral high frequency loss alone to profound bilateral loss. Progression or further deterioration and also fluctuation of loss are characteristic of hearing loss due to CMV infection.

In slide ten - for the rest of the talk, I would like to talk about studies at UAB and elsewhere in the last decade that have further characterized hearing loss due to congenital CMV infection. First is a more detailed description of the UAB cohort, the largest cohort to date that characterizes CMV related hearing loss.

Slide 11, in the cohort of 860 children 7.4% of the asymptomatic children and 40.7% of the symptomatic children had hearing loss following infection. Almost, half of the asymptomatic and over half of the symptomatic children had bilateral loss. High frequency loss (loss at 4000 to 12k Hz only) occurred in both groups, but was more commonly seen in asymptomatic children.

On slide 12, you can see that over 2/3 in both groups will eventually have severe to profound hearing loss.

And on slide 13, you can see that delayed onset hearing loss occurs in both asymptomatic and symptomatic children with the median age of delayed onset occurring in asymptomatic children

11 months later at 44 months, compared to 33 months for symptomatic children. However, you can see that the range for delayed onset loss is wide for both groups.

Slide 14, show that progressive loss occurs in equally in both groups. Fluctuating loss and improvement of loss occurs in both groups, however these types of loss occur more often in asymptomatic children. Next we have looked at predicting the timing of hearing loss due to CMV infection. We took a cohort of 388 children who were routinely screened for congenital CMV infection at University Hospital and followed in our clinics, and estimated the cumulative incidence of hearing loss in these children.

As you can see on slide 15, that when a cut off of greater than or equal to 30 dB is used for hearing loss, that 5.3% of the infants will have hearing loss by three months of age, and others continue to have some late or delayed onset loss, and by 72 months of age, 8.3% of children with congenital CMV infection will have a greater than or equal to 30 dB hearing loss diagnosed.

When you divide them out by symptomatic and asymptomatic as you can see in slide 16, that 16.5% of the symptomatic infants, and 2.9% of the asymptomatic infants will have hearing loss at birth. An additional 19.9% of symptomatic and 8.4% of asymptomatic children will have hearing loss identified by 72 months of age. We have looked at possible risk factors or factors that may enhance the risk to a child with congenital CMV infection going on to develop hearing loss.

On slide 17, symptoms at birth were evaluated on whether certain symptoms could predict which children would have hearing loss. On univariate analysis it appeared that intrauterine growth restriction and symptoms of disseminated infection were associated with hearing loss.

And not surprising on slide 18, can you see that intracranial calcifications were also associated with hearing loss. However as seen on slide 19, once factors were adjusted in a logistic regression model only, IUGR and petechiae remained associated with hearing loss in symptomatic infants. These findings suggest that disseminated infection at birth with or without CNS involvement is associated with hearing loss in symptomatic infants.

In slide 20, we have looked at asymptomatic infants to identify whether there are any maternal or perinatal factors that would be predictive of hearing loss. And as you can see in slide 20, most of them were African-American and cared for in a well baby nursery with a short nursery stay. Those with hearing loss and those without hearing loss did not differ for the traditional risk factors for hearing loss, however it appeared that those with hearing loss had slightly smaller birth weights and were more likely to be preterm.

However, as seen on slide 22, once race adjusted small for gestational age curves were used, the groups did not differ with respect to small for gestational age in fact the normal hearing group were slightly more likely to be SGA than those in the hearing loss group. Not surprisingly, maternal or perintal factors alone do not predict hearing loss in children with asymptomatic congenital CMV infection. Recently our group looked at the viral burden in infancy and hearing loss in children with congenital CMV infection, and as seen in slide 23, interestingly, those in the hearing loss group of asymptomatic children had higher mean amounts of CMV in their urine and also in their blood than asymptomatic children without hearing loss.

If you look at slide 24, all of the symptomatic infants had overall higher mean virus, those with hearing loss and those without did not differ. These findings, although the numbers are small, suggest that children with higher amounts of infectious CMV in their urine and CMV DNA in their blood during early infancy are more likely to have sensorineural hearing loss. We have also looked at the impact that universal newborn hearing screening has had on hearing loss due to CMV. In the past, and not surprising, risk-based auditory screening was not successful in identifying hearing loss due to CMV infection. Only 17.6% of the children with hearing loss due to congenital CMV infection were identified by risk criteria screening that was in place in University Hospital between 1995 and 1998.

And in slide 27, since the implementation of the universal newborn screening in 1998 here in Alabama, 84 infants have been identified with the infection. And only 42 received a newborn hearing screening (this number is low partly due to startup issues and the phasing in at the two local hospitals where the children came from)

But as seen in slide 28, overall, three of the 12 children, or 25%, with hearing loss due to CMV infection were identified by newborn screening. However, of the five not tested, three had documented delayed onset hearing loss, so 58% or seven of the 12 children with hearing loss due to CMV had delayed onset loss, so they were not expected to be detected on newborn hearing screening. So excluding these children, three of the five or 60% of the CMV children with hearing loss at birth were identified by newborn hearing screening.

Finally, I would like to comment on the relative contribution of CMV to childhood hearing loss. It has been difficult to ascertain since the date -- since to date there have not been any large scale population studies, that have included CMV screening of the newborn in the study of etiologic factors for childhood hearing loss. A few retrospective studies have attempted to assess the role of CMV in newborn hearing loss. As seen in slide 29, Peckham in 1987 looked at 1,644 children in London, aged six months to four years of age and had sensorineural hearing loss. These children were tested for CMV shedding and 13.2% with an unknown cause of hearing loss were found to be shedding virus. So this is not conclusive that they had congenital infection, but this was twice the rate found in other children with hearing loss of known causes and in children without hearing loss.

Using data from our follow up of CMV infants, we were able to identify 14 children with congenital CMV infection, and hearing loss out of 12,371 neonates screened for CMV, to estimate a hearing loss rate of 1.1 per thousand live births. And restricting to those infants with bilateral loss > 50 dB, the rate was 0.6 per 1000 births. If we surmise that the true population rate of hearing loss is 1 to 3 per 1000 births in this population then CMV may be the single most important cause of hearing loss in children within this population.

In slide 31, Barbi in a more recent study using nested PCR methodology on dried blood spots collected at birth were able to retrospectively identify CMV infection in children diagnosed with hearing loss. The study found that 24.7% of the children with hearing loss without other genetic causes, likely had hearing loss due to congenital CMV infection. There has only been one report from Sweden where the relative contribution of congenital CMV infection to bilateral profound hearing loss has been estimated in a population where CMV screening and newborn screening was routinely tested in all newborns. In this study, 10 out of 12,000 children had profound

hearing loss. Of these four were due to congenital CMV infection, four due to genetic causes, and two due to unknown causes.

In slide 34, if we estimate that 0.8% of infants born each year in the United States will have congenital CMV infection, and 3.9% will have hearing loss at birth, and if all of the infants were to receive newborn screening, then approximately 1,248 infants with congenital CMV infection and hearing loss will be identified before hospital discharge for a rate of .31 per thousand children. An expected additional 1,408 children with congenital CMV infection born each year will develop hearing loss later in the first years of life, for a rate of 0.35 per thousand children. So all of these are estimates from our best data available to date. However, more information is needed in other populations especially in the United States. So I leave you with, what is the true contribution of CMV in newborn and early childhood hearing loss in the United States? Thank you.

Jamie Elliott: Thank you, Dr. Fowler. Now we have Dr. Bracie Watson so talk about National Institutes of Health (NIH) initiatives.

Bracie Watson: Thank you. NIH wide there are about 178 funded CMV Research Grants; the majority are funded by NIAID. Other institutes with funded projects include NEI, NICHD, and NIDCD. Currently, there are no active solicitations specifically for CMV research applications.

NIDCD is committed to supporting CMV research related to our mission areas. NIDCD is funding studies that focus on understanding the role of congenital CMV in hearing loss. NIDCD currently funds 3 CMV research project grants (R01s), two supplements, and 1 CMV contract. Although our number of funded projects is small, you will learn later in this talk that our fiscal commitment for an institute of our size is quite large.

The direction that NIDCD has taken regarding CMV research has been guided by a workshop convened by NIDCD about three years ago to identify research needs related to CMV infection. For the sake of this discussion the recommendations made by the workshop participants were in three broad categories. Specifically, the need for 1). focused studies in humans, 2). molecular studies of the virus and host cells, and 3). studies involving the creation and use of animal models. A major outcome of the workshop was a contract which I will describe shortly.

To give you a flavor of the CMV research NIDCD is funding I will provide two examples.

Human studies of CMV—It has been shown that a significant proportion of children with congenital CMV infection (greater than 25%) are born to mothers with recurrent maternal infection. However, it is unknown what the relative contributions of re-infection with new CMV strains and re-activation of endogenous virus are to intrauterine transmission in women with pre-existing immunity. NIDCD is funding a study with the title: "Congenital CMV infection in Offspring of Immune Mothers". The goal of this study is to determine whether maternal re-infection results in an increased risk of intrauterine transmission of CMV in women with pre-existing immunity. Another goal is to characterize the antiviral antibody responses in seropositive women with and without intrauterine transmission.

Example of a study involving animal models: CMV exhibits strict species-specificity and therefore it is not possible to develop an animal model using human CMV virus. Still, animal

models that mimic the human condition may be instructive. NIDCD is funding a study with the title: "Congenital CMV Model of Auditory Pathology" The investigators have developed and are studying a SCID mouse model of intrauterine transmission of CMV. The mice are injected with CMV in the CSF and some affected offspring develop SNHL. The investigators confirmed for the first time congenital murine CMV (MCMV) infection in the developing auditory system. the investigators are now conducting basic mechanistic studies of how congenital and perinatal MCMV infection pathologically influences neuronal migration and apoptosis in the developing inner ear and auditory CNS.

The NIDCD CMV Contract— On a much larger scale NIDCD has recently awarded a contract to the University of Alabama at Birmingham (PI Suresh Boppana, Co-Investigator Karen Fowler) entitled: "The Natural History of CMV-related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn". The purpose of the contract is to address 1) the relationship between the presence of congenital CMV infection and long term-audiologic/otologic outcome, 2) the clinical validity and utility of CMV screening in the detection of permanent hearing impairment in the newborn, and 3) prediction of hearing impairment with onset during infancy or the early years of life. The CMV contract goals are 1) to correlate CMV status at birth with the presence of permanent/progressive sensorineural hearing loss, 2) to acquire data on the incidence, time course, and audiologic outcomes of CMV related hearing loss, and 3) to determine the extent to which CMV screening can improve detection and prediction of either existing or progressive hearing loss if combined with the metrics already in use for new born screening. The NIDCD fiscal commitment to this project is $15.6 million dollars over seven years and we will screen n = 100,000 newborns.

Jamie Elliott: Thank you, Dr. Watson. And finally, Dr. Ross, will give a brief summary of activities at CDC.

Dr. Ross: I'm going to give you a quick overview of the activities here at CDC regarding congenital CMV. We have a workgroup that is composed of two sub groups, one that focuses on epidemiology, and one that focuses on preventing and intervention.

The epidemiology sub group is working on a review of the literature that's similar to what is done in genomics called “HuGE” reviews. One of the goals of this review is to find out what the true prevalence rate is for congenital CMV because there is a wide range of prevalence. They will also be looking at cost studies, that is, what the cost burden of congenital CMV is.

The intervention and prevention sub group has submitted some questions to a survey called *HealthStyles*™, which is run by a company call Porter Novelli. You submit questions that you would like to ask the general public. The questions we submitted focus mainly on what women know about CMV, if they know anything, and what they might be willing to do to prevent congenital CMV infection. This is so can get of an idea of what prevention messages women who are pregnant will listen to and what kinds of behaviors they may be willing to change in order to prevent becoming infected shortly before and during pregnancy.

We also have a revised CMV web site that's looking really good. It's not ready, it's in clearance, but it will be ready soon, and it has a lot of information in it. As soon as that goes live, we'll send that out. It has some specific topics about CMV. Frequently asked questions, signs and symptoms, testing, diagnoses, treatment, up-to-date information on research on vaccines, and

there are references and resources. Some information such as what I'm talking about right now about CDC activities. There is also information for specific groups. For example, people who work with infants and children and people with weakened immune systems. People who are HIV positive who become infected with CMV often become very sick. There are specific links for CMV and pregnancy, and people who work in healthcare settings, et cetera. We also have a brochure on washing hands and some of the things that Mike Cannon was talking about. That is also in clearance. When it's available, we'll let you know, and that will be distributed free of charge.

Recently, on August 30th, we had a CDC-wide meeting with some invited outside experts, which included Karen Fowler who talked about CMV infection and hearing loss, and Stuart Adler who talked about screening issues, especially in women, and Robert Pass who talked on vaccine development. The main purpose of the meeting was to discuss priorities and new directions in prevention and screening for congenital CMV infection, and to get some interest in CMV infection among CDC scientists. We plan follow up with a paper on the proceedings from that paper and kind of broaden the scope of what we're doing. NCID (National Center for Infectious Diseases) also have several projects in progress. I just talked about the collaborative projects between NCBDDD and NCID.

At NCID Michael Cannon, who you just heard talk, recently published an article on the rationale behind hygiene to prevent CMV. And they're also doing a study on seroprevalence, based on a national survey, which will be coming out soon if I'm correct, is that right, Mike?

Michael Cannon: That's right.

Danielle Ross: They are looking at the feasibility of testing dried blood spots for screening and surveillance in newborns, which is being done in collaboration with Emory University and also the California State Department of Health. And finally, they're looking at CMV shedding and delayed hearing loss, which is being done in collaboration with the University of Alabama at Birmingham. So, if there's anything else you would like to add, Mike, this would be a good time.

Michael Cannon: You covered it really well.

Danielle Ross: And that's it for me. Jamie, do you want to take questions?

Jamie Elliott: Thank you, Dr. Ross, and thank you to all of the presenters for sharing with us. We have 15 minutes, which is a good amount of time left for questions, so if you have questions for any of the speakers, please go ahead now.

(Question and Answer from October 25th teleconference)

>> Hi, this is Sue from Maryland, and I wanted to know how you know that a person is shedding with CMV.

Michael Cannon: This is Mike Cannon, and do you mean what sort of diagnostic test you would use?

>> Yes.

Michael Cannon: again, it would be detection of the virus itself, either by growing the virus with a culture from whatever specimen you're looking in. Or PCR can be done as well.

Karen Fowler: This is Karen Fowler, and in addition, for a congenital infection, you diagnose it within the first two to three weeks of life. So that's the problem of getting a handle on the contribution of the hearing is because most children present later for the hearing loss, and if they weren't screened at birth, it's too late to determine what kind of infection.

Jamie: Any further questions?

>>This is Luella in Hawaii, and I was wondering if you could give me more information about detecting the feasibility of blood spot CMV testing.

Michael Cannon: Karen, did you want to address that?

Karen Fowler: You can go ahead.

Michael Cannon: So is your question, what are some published data for that?

>> Yes.

Michael Cannon: The -- let me see if I can pull up the references. The studies that have been published have been -- I don't know, there might be studies published from more than one lab, but the additional published studies were from a lab in Italy, and the first author of -- I think there are two or three papers, is Maria Barbi. And if you want to hang on, I can see if I can find the -- I can give you the references if you give me just a minute.

>> Thanks.

>> This is Shirley in Los Angeles, and one question that has arisen is whether we should be considering screening babies who screen positive on the newborn hearing screening for CMV. And of course nobody knows quite what to do if you do get a positive. Is anybody looking at anti-viral therapies or anyone doing work in that area?

Karen Fowler: I think there is a lot of controversy about anti-viral therapy. There's not a good anti-viral therapy. There's a toxic drug, and some people feel that if they have a child testing positive for CMV, they will consider treating the child with cyclovier. Here we don't do that, and we have children with severe symptoms, and in some of the randomized studies, looking at the oral dose of it or six weeks in the hospital. I know that Parkland Hospital in Dallas, they have -- what they do, when their babies fail the newborn hearing test, they do test them for CMV. And I'm trying to recall if their papers are out yet. This is a predominantly Hispanic population, and I know they have abstracts out. And the data is in press or processing if it's not out yet. And the first thorough -- that would be Shupe or Sanchez.

Michael Cannon: I have a couple of references about the blood spot methods that I could read off. The first is from September 2000 in the Journal of Clinical Virology, and the first author is Barbi. It's volume 17, and it starts on page 159. And a second one from that group is the Pediatric Infectious Disease Journal from 2003, and the first author is Barbi again, and the volume is
two, and it starts on page 39. From those references, they have a couple more you should be able to find anything else that has been published on it.

>> Thanks a lot.

Jamie Elliott: Great, anymore questions for any of our speakers? Okay, then I just want to say one more time, thank you very much for taking the time to speak with us today. And thanks to all of you who called in to participate. Transcripts will be made available on the CDC EHDI web site.

(Question and Answer from November 15, 2005 teleconference)

Jamie: We'll open the floor if anybody has any questions for any of our speakers, go ahead.

Speaker: This is a question from Minnesota. I think it's for Dr. Cannon. In one of your slides (the one that you commented that it was hard to see. It had the flow charts and it had the low income women--I think it was slide number 11. Low income women were on the right and high income women on the left or verse versa), can you comment on why the low income women have more immunity than higher income women?

Dr. Cannon: That's a really good question. And the answer is, we're not sure. We're recently -- these data are sort of older, but we're currently doing a study from The National Health and Nutrition Examination Survey, which is generalizable to the U.S. Population. We found sort of similar things that high income was associated with lower sero prevalence. But when you kind of pick it apart, of course it's not the money the women aren't getting infected from their money. It's a marker for other things, and some of the hypotheses are racial ethnic differences, which, you know, is hard to pin down.

Other hypotheses have to do with crowding in the home, factors related to being closer to more people. It could have to do with being more likely to care for young children, and it can also be due to breast feeding differences in the mothers of the people who are tested, so there are a number of hypotheses. It's probably a combination of all those things, but it is hard to pin down.

Speaker: Thank you. There was a big difference, so we wanted to ask.

Dr. Cannon: In the nationwide estimates, I think the differences weren't quite that much. But I think some with 20 to 25% difference— something like that. Yeah, there are big differences.

Speaker: I have a question I'd like to ask.

Jamie: Please go ahead. Who is your question for, sir?

Speaker: This is for Karen Fowler. My name is Dr. Walter Nance at the Medical College of Virginia. One of the criteria that has been traditionally used to identify and ultimately to estimate the genetic proportion of individuals with hearing loss is the frequency of multi-complex sibling relationships. That is to say a sibling relationship in which there are two or more affected infants. I wonder Dr. Fowler had you had a hundred infants with pro bands with CMV deafness, what percentage of them would have a similarly affected sibling?

Dr. Fowler: Dr. Nance, greetings. You're saying two siblings with congenital CMV infection?

Dr. Nance: Yes, I wonder how often that happens.

Dr. Fowler: I don't know. I can tell you from our experience of about 900 children from the 1960's to the present, we've only seen it occur two, maybe three times where we have two siblings that both had congenital CMV infections. Usually they were born within 24 months of each other. That's the only time that's been observed at UAB.

Not in the more recent years, but in the past, we were testing all the siblings back in the 1970s and 80s. There was one case I think in the 1970s where siblings both had congenital CMV infection. What's interesting about CMV is you can have twins and can you have discordant infection types— you could have one twin infected and not the other. That has happened, too. Also, I think in Italy, Dr. Gabrielli and colleagues reported a twin passing CMV in utero (they were able to document this) to the other twin. That's in a paper that was published in 2003 in the Journal of Microbiology. We saw in the 1990s a young woman who delivered an infant at 14 years of age and again at about 15 and a half years of age, and both infants were positive for CMV.

Dr. Nance: So you don't ordinarily counsel women that this is a substantial recurrence risk for them?

Dr. Fowler: No, we haven't.

Dr. Nance: Okay.

Jamie: Are there anymore questions for our presenters?

Speaker: I have a question.

Jamie: Please go ahead.

Speaker: Hi, this is Nancy Forward from Virginia Department of Health. I have a question. I guess it would be directed to Dr. Cannon. It has to do with your remarks about possible use of dried blood spot screening for congenital CMV. I wonder if you could tell me a little bit more - if you have a crystal ball, would you see that coming soon.
As I'm sure you're aware, many states, including Virginia, are gearing up to expand our current panel given the HRSA report on disorders and congenital diseases. I was wondering if you could speak more to that.

Dr. Cannon: Sure. Karen Fowler might be a better person to answer this. I think right now we're really trying to figure out questions of feasibility and also the utility. So what can you do if you screen? And we don't really have the data or the analyses, but it's likely that you could make a good argument for universal screening.

The main argument is that you identify a bunch of children who are at high risk of developing hearing loss at a subsequent full-time but that the universal hearing screening isn't going to identify them at birth. They are going to test normal at birth. The argument is. if you can identify them, can you follow them up and get them into early interventions which have been shown to improve hearing outcomes and similarly outcomes related to language, development and education? And additionally, it would be advantageous because you would avoid sort of the diagnostic odyssey that parents can go through that can be costly and very stressful when something is wrong with your child and you don't know what it is. And if you didn't have them screened at birth, there's really no way can you determine later on that it was caused by CMV.

I think those are the arguments for a screening program, but you have to prove that there's a feasible one that's relatively cost-effective, such as dried blood spots. As far as the question, *is that going to happen soon,* I think what I heard is that newborn screening is driven very much by advocacy. So we're hoping that there will be a good chunk of science in there, but the reality is it will probably happen if it gets pushed by advocacy groups and it may never happen if it doesn't. Did you want to add something to that, Karen?

Dr. Fowler: I'll only comment just briefly. I think we're at the point where everybody realizes that dried blood spots would be ideal. It's also working out the utility of the testing and what methods are best to use and how much that's going to cost to do that. We're going to be screening a hundred thousand infants using hopefully the dried blood spot on all hundred thousand as part of an NIH/NIDCD grant and trying to work out the details of that methodology as well. The CDC also has efforts underway, as we heard from Dr. Danielle Ross at both Emory and in California. So, I think we're trying to get the science answered, and then as Mike said, the issue of making it a national policy or public policy that goes beyond the science and that is a challenge we will face. But first we need to work out the science to determine if this is going to be a good screening technique or not.

Speaker: This is another question, a follow up of the last. This is Gill at Washington Children's Hospital for Dr. Cannon. In terms of antiviral drugs, what's the take on use of gancyclovir if an infant at birth is detected to have CMV? Will that prevent a resulting hearing loss?

Dr. Cannon: That's an excellent question, and I will give you my take and Karen you can add anything else.

Basically there's been one randomized controlled trial you might be familiar with, and what they showed, although, you know, there are some questions or at least I have a few questions as to the findings from that study. Basically they found an effect where severely affected children were enrolled into the trial. So they had severe neurological problems. What they found was that it appeared that those who were in the gancyclovir group had less likelihood of developing hearing loss if they didn't have any to start with or for having their hearing loss progress if they had hearing loss to begin with. However, the treatment was quite toxic and a number of infants had to be taken off of it.

So the bottom line is it's only really been tested in very severely affected infants. The effect they were looking at really had to do only with hearing loss and not other outcomes, but it appears that it may have some preventive effect as far as not letting things get worse. It doesn't seem that there's evidence that hearing will improve because of the treatment. But as far as starting that sort of thing on a wider scale among asymptomatic infants, I believe a trial is going on to look at that. But that's a bigger question mark, because the treatment is just relatively toxic and hard to take.

Gill Washington: Thank you.

Jamie: We have about five minutes left for questions, if anyone has anything to ask.

Speaker: Yes, I have a question. This is Dr. Matthews from New Mexico. In terms of— it always seemed to me that the women who are at high risk of getting it are always in prime child bearing age because they either have young children or children in day-care bring it home to the family or they're working in child care settings. Do you have any statistics or any studies on what the effectiveness is of preventative measures like taking sero-negative child care workers and who are using protective measures— what their sero conversion rates are?

Dr. Cannon: This is Mike Cannon. There is some evidence. It's limited, but basically there's been some sort of randomized trials for interventions, and they've kind of had mixed results.

The first one found that those who received the intervention for improved hygiene, had lower rates of sero conversion, but not statistically so. But there was also a non-randomized group of pregnant women, and they did have statistically lower rates of sero conversion, which led the authors to conclude that being pregnant was important. In other words, that motivation mattered as far as avoiding infection.

The second trial was more mixed, and it wasn't clear that it was effective. I think the kind of take home message, in my opinion, is that there is lots of evidence that if women actually follow these sorts of improved hygiene that they should be able to reduce their risk. And most people would agree with that. The real question is, can you devise interventions or messages or that sort of thing that actually induce women or are effective at getting women to make those changes while they're pregnant? So we're optimistic. That's the sort of nutshell answer for you, but I can go through all the evidence in the paper that I cite in the slides if you want the longer answer.

Dr. Matthews: No, that's good. But it seems like considering that a lot of women don't know they're pregnant until they're further along than you would like, that we may need vaccines rather than preventative measures.

Dr. Cannon: Well, I think no one is going to disagree with you there. We mostly just argue that the only alternative to waiting and waiting for a vaccine is to do what we can in the interim. So, yes, I agree. It would be great to have a vaccine, but we're hoping we can do something about this in the meantime.

Jamie: Do we have any more questions for the presenters? Alright. Then I want to be sure to thank our presenters for taking the time out to speak to us on this topic.

Thank you for participating in today's call. We will have a transcript available of the call within a month.

I wanted to let you know that our next conference call will likely be in the new year, as we don't have one scheduled for December.

Thank you for joining us and special thanks to our speakers today.

[end of call.]